Fertility Control with Long-acting Injectable Steroids
A Preliminary Report

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BECAUSE of the dangers to world society from the explosive growth of population, particularly in the developing countries, the search must continue for effective, safe, and acceptable technics of fertility control suitable for illiterate or poorly educated rural populations. In the developed nations and among educated women, the effectiveness of oral contraceptive agents is astounding; yet even here the limiting factor on effectiveness is the reliability of medication intake. In many parts of the world, experience has shown that effectiveness of oral contraceptives falls far below the level which has been achieved in the developed nations. All too frequently these failures are followed by criminal abortion, and the resulting morbidity is one of the major causes of gynecologic hospitalization in some countries. Since even rural populations are accustomed to injections for protection against various diseases, it was thought that an injectable method to control fertility would be readily acceptable if the action of the agent were sufficiently prolonged.

MATERIALS AND METHODS

Two groups of patients were used in this preliminary study. Group M (Mexico) consisted of 151 multiparous women who came to a family-planning clinic seeking control of their fertility. Of the 151, 111 were menstruating regularly and 40 were in postpartum amenorrhea and lactating. Group C (Chile) consisted of 159 patients, of whom 135 were postpartal and 24 were postabortal. Of these women, 112 were still amenorrheic and 100 were lactating.

The injectable agent was medroxyprogesterone acetate (MPA), a compound which has been used since 1958 in over 500,000 patients in the United States for a variety of indications. It was given either alone, in doses ranging from 200 to 1000 mg., or as a combination of medroxyprogesterone acetate, 150 mg., with estradiol polyphosphate, 40 mg. The combination was given to 99 women of Group M at intervals of 3 months. Nineteen women received 200 mg. MPA per injection, 91 received 250 mg., 59 received 500 mg., and 43 received 1000 mg. per injection. Pelvic examinations, vaginal cytologic studies, and histologic evaluation of the endometrium were performed at frequent intervals when possible.

RESULTS

At the time of the present report, 1638 woman-months of experience have been accumulated. From the point of view of effectiveness, this experiment is as yet too small to be significant, particularly since a large proportion of the women started treatment during postpartum amenorrhea, and 140 of them were lactating. However, pregnancies have occurred in only 3 women, who became pregnant 10–11 months after a single injec-

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Submitted for publication Apr. 22, 1966.

tion of MPA. Thirty-five women of Group M were maintained under observation for only 6 months, and were then given an oral contraceptive to which they responded in the usual fashion.

The major undesirable effect of the steroid injection was a complete disorganization of the menstrual pattern, with intermittent periods of amenorrhea, spotting, or bleeding. The latter, however, was seldom heavy. There was no appreciable difference in the bleeding patterns of women receiving 500 or 1000 mg. of MPA alone, or 150 mg. combined with estradiol polyphosphate. For many women, this unpredictable menstrual behavior was indeed disturbing, because they feared that the amenorrhea indicated pregnancy; for others the irregular bleeding implied some serious disturbance. Accordingly, to 25 patients of Group C given MPA alone, a supplementary course of natural (estrone sulfate) or synthetic (ethynyl estradiol, mestranol) estrogen was administered for 7–10 days each month. By individual adjustment of this dose regular uterine bleeding with satisfactory quantity and duration was re-established. The optimum dosage of supplementary estrogen has yet to be established, but this small series at least indicates a way in which the menstrual irregularity caused by MPA alone can be overcome. The use of an oral agent to regularize cycles is, of course, fundamentally different from the taking of an oral contraceptive: With MPA, effectiveness is maintained regardless of patient reliability in taking pills, whereas with oral contraceptives reliability is the determining factor in effectiveness.

Vaginal cytologic studies after some months of medication, with or without estradiol polyphosphate, invariably showed a marked decrease in the karyopyknotic index, which frequently approached zero. In addition, there were marked regressive changes, with the superficial cells being small and inactive in appearance. Endometrial evaluation was very difficult with MPA alone, since it was usually impossible to get sufficient tissue by biopsy for adequate reading. The endometrial glands were extremely regressed, small, and inactive; this was even more evident when 500 or 1000 mg. of MPA alone was used than with the inclusion of estradiol polyphosphate. The stroma with MPA plus estradiol polyphosphate occasionally showed moderate edema; at times there were small areas of decidual change, but usually the endometrial tissue showed the intense regression and dense fibrous stroma of an atrophic, postmenopausal endometrium.

Spontaneous return of menstruation has been studied in only a limited number of subjects. Table 1 shows the results of a single-injection study of 26 patients from Group M. Half had received 500 mg. and half 1000 mg., intramuscularly.

Lactation was evaluated with considerable interest, since in many regions the mother's milk comprises virtually the entire food intake of the infant during the first year

TABLE 1. INTERVAL BEFORE SPONTANEOUS RETURN OF MENSTRUATION IN 26 PATIENTS AFTER INJECTION OF MEDROXYPROGESTERONE ACETATE

Months after injection	*Patients receiving 500 mg.*		*Patients receiving 1000 mg.*	
	No.	*Cumulative %*	*No.*	*Cumulative %*
6	5	38.4	—	—
7	4	69.2	8	61.5
8	3	92.3	2	76.9
9	1	100.0	2	92.3
10	—	—	1	100.0
TOTAL	13		13	

of life. In neither series (M or C) was any significant diminution in lactation observed, and the addition of estradiol polyphosphate to the MPA had no perceptible effect. In Group C it was frequently reported as heavier and of longer duration than previous lactations.

Side effects such as headache, dizziness, and other nonspecific symptoms were reported by a few patients. However, since placebos were not used, it is not possible to assess their relationship to the medication at the present time. Certainly, they constituted no significant factor in patient acceptance. In Group M, most of the subjects were shifted automatically to an oral contraceptive after 6 months' trial with MPA alone. It is worth noting that 30 women voluntarily requested a second injection, and there were other spontaneous requests from friends and relatives of the test subjects.

Three subjects from Group C became pregnant 10–11 months after a single injection of MPA. In this study it was then decided to repeat the injections at 6-month intervals, to insure a safe period of 2 or 3 months if the subject failed to report on schedule for the next injection. This interval seems to be satisfactory but should be explored further.

DISCUSSION

These preliminary studies serve to delineate the problems and possibilities of long-acting injectable progestational steroids for fertility control. A valid assessment of effectiveness will require about 10,000 woman-months of experience, but the present findings of long-duration fertility inhibition, followed by return of spontaneous menses and fertility, outline the parameters which will have to be explored.

In addition to those concerning effectiveness, many important questions are raised by such a regimen, and will require careful study. The rebound of pituitary gonadotropin secretion, of ovarian function, and of endometrial response will have to be explored, both with and without cyclic estrogen supplementation. The degree of suppression of pituitary FSH and/or LH will have to be explored, as will the residual function of the ovary—i.e., the levels of estrogen which may persist during therapy. Certainly, if MPA produces a shutdown of steroid hormone synthesis, estrogen supplementation will become increasingly important if long-term use is contemplated.

SUMMARY

Medroxyprogesterone acetate in single intramuscular injections ranging from 200 to 1000 mg., with and without supplemental estrogen, was tested in 310 women as a means of fertility control. During 1638 woman-months of use, no pregnancies occurred until 10–11 months after a single injection. The menstrual rhythm was entirely disorganized, but a brief supplemental course of oral estrogen reinstituted an acceptable, cyclic withdrawal bleeding. Other side effects were insignificant, and there was no interference with lactation.

This approach is worthy of expanded, intensive investigation as a new departure in fertility control.

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